Mark copy.

LOMOND & ARGYLL PRIMARY CARE NHS TRUST

Mid Argyll & Mental Health Directorates

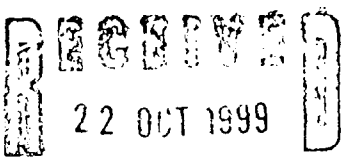
Direct Telephone: 01546 604908
Direct Facsimilie: 01546 606452
E-mail: angus.mackay@aandb.scot.nhs.uk

ARGYLL & BUTE HOSPITAL
LOCHGILPHEAD
ARGYLL PA31 8LD

Our Ref AVPM/DAP

20 October 1999

Dr J Dunne
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ



Dear Julia

Clinical Investigation of Medicinal Products in the Paediatric Population

I read with interest this paper which is on the agenda for CSM on 28th October 1999. From a psychopharmacological point of view this is an extremely important area and I would certainly echo, and if possible emphasise, the points made in paragraphs 2.4.3 and 2.6.4 about the vital necessity of monitoring cognitive and behavioural safety during the investigation of psychoactive preparations. It is extremely important that long-term studies of safety in these domains are incorporated in any evaluation programme.

I would also like to make the following specific points;

Paragraph 2.5.3
It is stated that the period extending from 28 days to 23 months of life is "a period of CNS maturation associated with completion of myelination". This implies that all myelination is complete by the end of two years but this is not the case. Associated, to a large extent, with recent research on the neurodevelopmental aspects of schizophrenic illness, there seems to be quite a body of evidence to suggest that myelination in some limbic circuits (at least) go on until early adulthood. I am thinking particularly about tracts which connect the dorsolateral prefrontal cortex with medial temporal lobe and other structures. Here, the work of Weinberger and others at NIMH is noteworthy. In addition to the question of myelination, there is increasing evidence that gross neuronal organisation changes well into adolescence, seen as developmental changes in cerebral asymmetry, no doubt under the control of various brain-derived growth factors and these are potentially amenable to modification by CNS-active drugs. A noteworthy expert in

I

00D-1223

C 8

this area is Professor Tim Crow at Oxford. The point being that neurodevelopmental processes are occurring well into late adolescence.

Paragraph 2.5.5
Referring to adolescence, the paper does refer to "evolving cognitive and emotional changes", which is quite right, and I have concern about the vulnerability of developing brains to CNS drugs, even if the gross hard-wiring is in place. Synaptic plasticity is a life-long property but is undoubtedly more significant in adolescence in terms of effects on the facilitation of certain circuits responsible for cognition and behaviour which, once established at critical times, would persist long-term. Hebb's principle is long-established; that synaptic "strength" is proportional to the amount of traffic across a synapse. Any drug which affected receptor occupancy by neurotransmitter, especially in the long term in the developing brain, could have potent effects on the life-long performance of a neuronal system.

Forgive me for taking a long-winded way of emphasising the need for caution over the use of psychoactive drugs in young brains, but I feel that this point deserves emphasis.

With kind regards

Yours sincerely

Dr A V P Mackay
Physician Superintendent/Clinical Director

cc Professor A M Breckenridge